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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/069,251	06/06/2002	Keizo Inoue	04853.0089	7644

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EXAMINER	
BERTOGLIO, VALARIE E	
ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 11/29/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/069,251	INOUE ET AL.	
	Examiner	Art Unit	
	Valarie Bertoglio	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 October 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *37-48* is/are pending in the application.

4a) Of the above claim(s) *49-51* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *37-48* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *02/22/2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's reply dated 10/06/2004 has been received. Claims 1-36 have been cancelled. Claims 37-51 have been added. Claims 49-51 are drawn to a non-elected invention and are withdrawn from examination. Claims 37-51 are pending and claims 37-48 are under consideration in the instant office action.

Election/Restrictions

Applicant has requested a rejoinder of Groups I and III set forth in the restriction requirement mailed 10/21/2002. Applicant elected Group I without traverse in the reply dates XYZ. This restriction is maintained for reasons set forth in the restriction requirement mailed XYZ. Group I is directed to a product and Group III is directed to a process of using said product. The knockout animal of Group I has uses other than that of Group III and the methods of Group III can be performed using a different animal. Therfore, the restriction is maintained and claims 49-51, drawn to the non-elected invention will not be examined in the instant office action.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 37-48 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a transgenic mouse whose genome comprises a homozygous disruption of the endogenous α-TTP gene wherein α -TTP is not expressed and said transgenic mouse exhibits non-detectable levels of plasma α -tocopherol and for a transgenic mouse whose

genome comprises a heterozygous disruption of the endogenous α -TTP gene wherein α -TTP is not expressed from the disrupted allele and said transgenic mouse exhibits about one-half the plasma level of α -tocopherol and while being 1nabling for a method of screening test compounds for treating disease characterized by decreased plasma vitamin E, does not reasonably provide enablement for the claimed mouse wherein α-TTP expression is inhibited to varying degrees from the disrupted allele or wherein the claimed mouse is chimeric or methods of screening test compounds for treating any disease characterized by oxidative impairment . The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Applicant's arguments have been thoroughly considered and are found partially persuasive with respect to certain aspects of the rejection as set forth below.

The aspect of the rejection with respect to knockout of a non-endogenous α -TTP gene is withdrawn in light of Applicant's amendments to the claims.

With respect to the rejection based on failure to enable the use of the heterozygous mouse, the rejection is withdrawn. Applicant has argued that the heterozygous mouse encompassed by claims 46-48 have use in making the claimed homozygote. While this argument is not persuasive to the extent that use of a heterozygote to make a homozygote is not a specific use, the mouse is useful for screening agents that increase plasma α -tocopherol levels in the same way that the homozygous is useful. The difference in usefulness of the heterozygote and homozygote is that the homozygote exhibits failure to maintain pregnancy in females. However,

this phenotype is actually more time-consuming to use in a screening assay than assaying plasma α -tocopherol. Therefore, use of both the heterozygote and the homozygote are enabled.

With respect to the breadth of the claims encompassing varying degrees of inhibition of α -TTP expression from the disrupted α -TTP allele, Applicant has argued that the previous rejection set forth on pages 6-7 pf the previous office action are not applicable to the newly added claims. Applicants note that the new claims do not include the term knockout.

In response, claims 37-48 are drawn to a transgenic mouse whose genome comprises a homozygous disruption of the endogenous α -TTP gene, wherein α -TTP expression in inhibited. This limitation encompasses any degree of inhibition of expression from the α -TTP gene. The specification teaches deletion of exon 1 of the α -TTP gene. The specification has not taught any other type of disruption to the α -TTP gene and has not provided any structural or functional characteristics with respect to α -TTP that would enable the skilled artisan to determine what disruptions would cause varying levels of α -TTP expression other than the disruption taught in the instant specification. Deletions within the α -TTP can be made such that no functional α -TTP protein is made by deleting at least the region taught by the specification. However, it would not be obvious to the skilled artisan how to disrupt the α -TTP gene or surrounding DNA to lower levels of expression of α -TTP to any level other than null. While the claims no longer recite the term "knockout", the claims read on a genera of disruptions that are not supported by the specification. Use of the term knockout in the previous set of claims was inconsistent with the genera of resulting phenotypes encompassed to the extent that the specification failed to enable making a knockout that was not a null, however, removal of this term fails to render the specification enabling for varying levels of α -TTP expression for the reasons set forth above.

With respect to the chimeric mice of claims 41-45, applicant has not specifically provided any arguments. However, Applicants arguments with respect to the use of the heterozygous mice in generating homozygous mice pertain to the extent that the chimeric mouse can be used as an intermediate to generate heterozygous and homozygous mice. This does not constitute a specific utility and the specification provides no other use for the chimeric mice. Any chimeric mouse comprising germline cells whose genome comprises a gene disruption can be used to make a transgenic mouse. This use is not specific to the claimed chimeric mouse. The specification provides no other use for the claimed chimeric mice and therefore fails to teach the skilled artisan how to use them. As set forth in the previous office action, the state of the art at the time of filing held that the phenotype of chimeric mice is highly unpredictable. It cannot be determined, a priori, what cells or how many cells will comprise a disruption. Furthermore, the disruption will be heterozygous in the cells that do comprise the disruption. As a result, it cannot be predicted that any reasonable number of mice, if any at all, would exhibit a useful phenotype. Furthermore, any mouse that does have a phenotype (i.e. reduced levels of plasma α -tocopherol) is not readily reproducible. To determine that the claimed chimeras would have a specific use, the skilled artisan would have to perform undue experimentation to determine that chimeras, which include mice comprising a heterozygous disruption of the α -TTP gene in a single cell, exhibit a phenotype. The specification offers no guidance as to whether the claimed chimeras exhibit a useful phenotype, what that phenotype is, or how to make chimeras that would exhibit such a phenotype (i.e. how many cells and which cells require α -TTP gene disruption). Therefore, in light of the unpredictability of phenotype for chimeric mice and the lack of guidance in the specification with respect to the phenotype of the chimeric mice it would require

undue experimentation for the skilled artisan to determine how to make the claimed chimeras such that they have a specific use and how to use them.

The previously pending claims were also rejecting because the breadth of the claims included mice exhibiting any vitamin E deficiency phenotype (see pages 4-5 of the previous office action). Applicant argues that the newly added claims do not encompass this broad genus of phenotypes. However, claims 41 and 43-45 are drawn to mice exhibiting any vitamin E deficiency phenotype, which includes phenotypes other than failure of female mice to maintain pregnancy (see Cavalier, 1998; Thomas, 1993). Therefore, the rejection is maintained as it applies to claims 41 and 43-35.

Therefore, in light of the breadth of the claims with respect to the level of α-TTP expression, the phenotypes exhibited by the claimed mice and the disease states encompassed by the claims as well as the state of the art with respect to the predictability pf phenotype in transgenics and role of vitamin E in all manifestations of oxidative stress, it would require undue experimentation for the skilled artisan to implement the claimed invention with a reasonable degree of success.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

The rejection of claims 21-36 is withdrawn in light of Applicant's cancellation of the claims. The rejection is not applicable to the newly added claims.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Valarie Bertoglio whose telephone number is (571) 272-0725. The examiner can normally be reached on Mon-Thurs 5:30-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson can be reached on (571) 272-0804. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Valarie Bertoglio
Examiner
Art Unit 1632

Joe Woitach
AU1632